CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074534

Trade Name : SUFENTANIL CITRATE INJ 50MG/ML

Generic Name: Sufentanil Citrate Injection USP 50mg/ml

Sponsor :Abbott Laboratories

Approval Date: December 11, 1996

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074534

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Pharmacology Review(s)				
Statistical Review(s)				
Microbiology Review(s)				
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Bioequivalence Review(s)	X			
Administrative Document(s)				
Correspondence				

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074534

APPROVAL LETTER

ANDA 74-534

DEC 1 1 1996

Abbott Laboratories
Attention: Thomas Willer, Ph.D.
200 Abbott Park Road
D-389, Bldg. AP30
Abbott Park, Illinois 60064-3537

Dear Sir:

This is in reference to your abbreviated new drug application dated August 15, 1994, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Sufentanil Citrate Injection USP, 50 mcg (base)/mL.

Reference is also made to your amendments dated September 3 and 27, October 9, and December 5, 1996.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Sufentanil Citrate Injection USP, 50 mcg (base)/mL to be bioequivalent and, therefore, therapeutically equivalent to the listed drug Sufenta® Injection, 50 mcg/mL of Janssen Pharmaceutica Inc.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/S/ 12/11/96

Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074534

FINAL PRINTED LABELING

5 mL 10 Fliptop Vials NDC 0074-3382-25

SUFENTANIL CITRATE Inj., USP

C II

250 mcg* **(50 mcg/mL)***

WARNING: MAY BE HABIT FORMING.

Protect from light.
Retain in carton until time of use.
For Intravenous Use.

ABBOTT LABORATORIES, NORTH CHICAGO, IL 60064, USA

*Each mL contains sufentanil citrate equivalent to 50 mcg sufentanil. May contain sodium hydroxide and/or hydrochloric acid for pH adjustment. pH 4.2 (3.5 to 6.0).

Sterile, nonpyrogenic.

USE ASEPTIC TECHNIQUE:
Remove cover from fliptop vial and cleanse stopper with antiseptic.

Usual dosage: See insert. Discard unused portion.

Store at controlled room temperature 15° to 30°C (59° to 86°F).

Caution: Federal (USA) law prohibits dispensing without prescription.

++300743382252Z

08-7645-2/R1-1/96

Printed in USA

5 mL 10 Fliptop Vials NDC 0074-3382-25

SUFENTANIL CITRATE Inj., USP

C II

250 mcg* (50 mcg/mL)*

WARNING: MAY BE HABIT FORMING.

Protect from light. Retain in carton until time of use.
For Intravenous Use.

ABBOTT LABORATORIES, NORTH CHICAGO, IL 60064, USA

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5 mL 10 Fliptop Vials NDC 0074-3382-25

SUFENTANIL CITRATE Inj., USP

C II

250 mcg* (50 mcg/mL)*

WARNING: MAY BE HABIT FORMING.

Protect from light.
Retain in carton until time of use.
For Intravenous Use.

ABBOTT LABORATORIES, NORTH CHICAGO, IL 60064, USA

5 mL 10/NDC 0074-3382-25

SUFENTANIL CITRATE Inj., USP C II

250 mcg*

(50 mcg/mL)*

ABBOTT LABS, NORTH CHICAGO, IL 60064, USA

5 mL

SUFENTANIL CITRATE
Injection, USP

250 mcg
(50 mcg/mL)

WARNING: May be habit forming.

ABBOTT LABS, N. CHICAGO, IL 60064, USA

NDC 0074-3382-05

For I.V. Use. Protect from light. Retain in carton until time of use.

Caution: Federal (USA) law prohibits dispensing without prescription.

06-7918-2/R1-1/96

2 mL 10 Fliptop Vials NDC 0074-3382-22

SUFENTANIL CITRATE Inj., USP

(50 mcg/mL)*

WARNING: MAY BE HABIT FORMING.

Protect from light. Retain in carton until time of use. For Intravenous Use.

ABBOTT LABORATORIES, NORTH CHICAGO, IL 60064, USA

*Each mL contains sufentanil citrate equivalent to 50 mcg sufentanil. May contain sodium hydroxide and/or hydrochloric acid for pH adjustment. pH 4.2 (3.5 to 6.0).

Sterile, nonpyrogenic.

USE ASEPTIC TECHNIQUE.

Remove cover from fliptop vial and cleanse stopper with antiseptic.

Usual dosage: See insert. Discard unused portion.

Store at controlled room temperature 15° to 30°C (59° to 86°F).

Caution: Federal (USA) law prohibits dispensing without prescription.

++300743382222W

08-7644-2/R1-1/96 Printed in USA

2 mL 10 Fliptop Vials NDC 0074-3382-22

SUFENTANIL CITRATE Inj., USP

(50 mcg/mL)*

WARNING: MAY BE HABIT FORMING.

Protect from light. Retain in carton until time of use.

For Intravenous Use.

ABBOTT LABORATORIES, NORTH CHICAGO, IL 60064, USA

2 mL 10/NDC 0074-3382-22

SUFENTANIL CITRATE Inj., USP

(50 mcg/mL)*

ABBOTT LABS, N. CHGO., IL 60064, USA

2 mL NDC 0074-3382-02

SUFENTANIL CITRATE Inj, USP

[redacted]

(50 mcg/mL)

WARNING: May be habit forming.

For I.V. Use. 06-7917-2/R1-1/96

ABBOTT LABORATORIES, N. CHICAGO, IL 60064, USA

1 mL 10 Fliptop Vials NDC 0074-3382-21

SUFENTANIL CITRATE Inj., USP (II)

50 mcg* **(50 mcg/mL)***

WARNING: MAY BE HABIT FORMING.

Protect from light. Retain in carton until time of use. For Intravenous Use.

ABBOTT LABORATORIES, NORTH CHICAGO, IL 60064, USA

*Each mL contains sufentanil citrate equivalent to 50 mcg sufentanil. May contain sodium hydroxide and/or hydrochloric acid for pH adjustment. pH 4.2 (3.5 to 6.0).
Sterile, nonpyrogenic.
USE ASEPTIC TECHNIQUE.
Remove cover from fliptop vial and cleanse stopper with antiseptic.
Usual dosage: See insert. Discard unused portion.
Store at controlled room temperature 15° to 30°C (59° to 86°F).
Caution: Federal (USA) law prohibits dispensing without prescription.

++3007433822 12V

08-7643-2/R1-1/96 Printed in USA

1 mL 10 Fliptop Vials NDC 0074-3382-21

SUFENTANIL CITRATE Inj., USP (II)

50 mcg* **(50 mcg/mL)***

WARNING: MAY BE HABIT FORMING.

Protect from light. Retain in carton until time of use.

For Intravenous Use.

ABBOTT LABORATORIES, NORTH CHICAGO, IL 60064, USA

1 mL 10/NDC 0074-3382-21

SUFENTANIL CITRATE Inj., USP (II)

50 mcg* **(50 mcg/mL)***

ABBOTT LABS, N. CHGO., IL 60064, USA

1 mL NDC 0074-3382-01

SUFENTANIL CITRATE Inj., USP

50 mcg

(50 mcg/mL)

C II

WARNING: May be habit forming.

For I.V. Use. 06-7914-2/R1-1/96

ABBOTT LABORATORIES, N. CHICAGO, IL 60064, USA

5 mL 10 Ampuls NDC 0074-3380-35

SUFENTANIL CITRATE Injection, USP

250 mcg*

(50 mcg/mL)*

WARNING: MAY BE HABIT FORMING.

*Each mL contains sufentanil citrate equivalent to 50 mcg sufentanil. May contain sodium hydroxide and/or hydrochloric acid for pH adjustment. pH 4.2 (3.5 to 6.0). Sterile, nonpyrogenic.

Usual dosage: See insert.

Store at controlled room temperature 15° to 30°C (59° to 86°F).

Caution: Federal (USA) law prohibits dispensing without prescription.

Protect from light. Retain in carton until time of use.

For your convenience in recording narcotic use

	INITIAL/DATE		INITIAL/DATE
1		6	
2		7	
3		8	
4		9	
5		10	

08-7642-2/R1-1/96

Printed in USA

++300743380352Y

INSPECT™ Tamper Evident Carton

Directions for ampul verification:

1. Upon receipt, inspect carton. Verify tamper evident tape is not broken. Do not break tape prior to dispensing.
2. Lift front flap. Verify carton contains 10 ampuls. Reclose the flap.

5 mL 10 Ampuls NDC 0074-3380-35

SUFENTANIL CITRATE Inj, USP

250 mcg*

(50 mcg/mL)*

WARNING: MAY BE HABIT FORMING.

5 mL 10 Ampuls NDC 0074-3380-35

SUFENTANIL CITRATE Inj, USP

250 mcg*

(50 mcg/mL)*

WARNING: MAY BE HABIT FORMING.

Protect from light. Retain in carton until time of use.

NDC 0074-3380-35

5 mL 10 Ampuls

SUFENTANIL CITRATE Injection, USP

250 mcg*

(50 mcg/mL)*

WARNING: MAY BE HABIT FORMING.

5 mL 10 Ampuls NDC 0074-3380-35

SUFENTANIL CITRATE Injection, USP

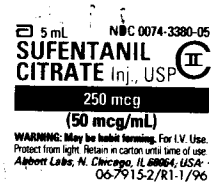
250 mcg*

(50 mcg/mL)*

WARNING: MAY BE HABIT FORMING. Protect from light. Retain in carton until time of use.

For Intravenous Use.

ABBOTT LABORATORIES, NORTH CHICAGO, IL 60064, USA


5 mL
NDC 0074-3380-05
SUFENTANIL
CITRATE Inj., USP
C II
250 mcg
(50 mcg/mL)
WARNING: May be habit forming. For I.V. Use.
Protect from light. Retain in carton until time of use.
Abbott Labs, N. Chicago, IL 60064, USA
06-7915-2/R1-1/96

2 mL 10 Ampuls

SUFENTANIL CITRATE Injection, USP

[redacted]

(50 mcg/mL)*

WARNING: MAY BE HABIT FORMING.

NDC 0074-3380-32

Protect from light.
Retain in carton until time of use.

CII

* Each mL contains sufentanil citrate equivalent to 50 mcg sufentanil. May contain sodium hydroxide and/or hydrochloric acid for pH adjustment. pH 4.2 (3.5 to 6.0). Sterile, nonpyrogenic.

Usual dosage: See insert.

Store at controlled room temperature 15° to 30°C (59° to 86°F).

Caution: Federal (USA) law prohibits dispensing without prescription.

For your convenience in recording narcotic use

	INITIAL/DATE		INITIAL/DATE
1		6	
2		7	
3		8	
4		9	
5		10	

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08-7641-2/R1-1/96 Printed in USA

2 mL 10 Ampuls SUFENTANIL CITRATE Inj, USP [redacted] (50 mcg/mL)* WARNING: MAY BE HABIT FORMING. NDC 0074-3380-32 CII

2 mL 10 Ampuls SUFENTANIL CITRATE Injection, USP [redacted] (50 mcg/mL)* WARNING: MAY BE HABIT FORMING. Protect from light. Retain in carton until time of use. NDC 0074-3380-32

***INSPECT*™ Tamper Evident Carton**

Directions for ampul verification:
1. Upon receipt, inspect carton. Verify tamper evident tape is not broken. Do not break tape prior to dispensing.
2. Lift front flap. Verify carton contains 10 ampuls. Reclose the flap.

2 mL 10 Ampuls

SUFENTANIL CITRATE Injection, USP CII

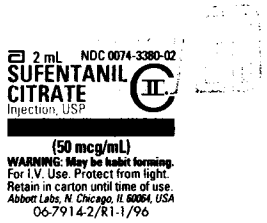
[redacted]

(50 mcg/mL)*

WARNING: MAY BE HABIT FORMING. Protect from light. Retain in carton until time of use.

For Intravenous Use.

ABBOTT LABORATORIES, NORTH CHICAGO, IL 60064, USA


2 mL NDC 0074-3380-02
SUFENTANIL CITRATE
Injection, USP
C II
(50 mcg/mL)
WARNING: May be habit forming.
For I.V. Use. Protect from light.
Retain in carton until time of use.
Abbott Labs, N. Chicago, IL 60064, USA
06-7914-2/R1-1/96

1 mL 10 Ampuls

SUFENTANIL CITRATE Injection, USP

50 mcg*

(50 mcg/mL)*

NDC 0074-3380-31

Protect from light.
Retain in carton until time of use.

WARNING: MAY BE HABIT FORMING.

* Each mL contains sufentanil citrate equivalent to 50 mcg sufentanil. May contain sodium hydroxide and/or hydrochloric acid for pH adjustment. pH 4.2 (3.5 to 6.0). Sterile, nonpyrogenic.

Usual dosage: See insert.

Store at controlled room temperature 15° to 30°C (59° to 86°F).

Caution: Federal (USA) law prohibits dispensing without prescription.

For your convenience in recording narcotic use

	INITIAL/DATE		INITIAL/DATE
1		6	
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3		8	
4		9	
5		10	

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08-7640-2/R1-1/96 Printed in USA

1 mL 10 Ampuls NDC 0074-3380-31 SUFENTANIL CITRATE Inj., USP 50 mcg* (50 mcg/mL)* WARNING: MAY BE HABIT FORMING.

1 mL 10 Ampuls NDC 0074-3380-31 SUFENTANIL CITRATE Inj., USP 50 mcg* (50 mcg/mL)* WARNING: MAY BE HABIT FORMING.

1 mL 10 Ampuls NDC 0074-3380-31 SUFENTANIL CITRATE Injection, USP 50 mcg* (50 mcg/mL)* WARNING: MAY BE HABIT FORMING. Protect from light. Retain in carton until time of use.

***INSPECT*™ Tamper Evident Carton**

Directions for ampul verification:
1. Upon receipt, inspect carton. Verify tamper evident tape is not broken. Do not break tape prior to dispensing.
2. Lift front flap. Verify carton contains 10 ampuls. Reclose the flap.

1 mL 10 Ampuls NDC 0074-3380-31 SUFENTANIL CITRATE Injection, USP 50 mcg* (50 mcg/mL)*

WARNING: MAY BE HABIT FORMING. Protect from light. Retain in carton until time of use.
For Intravenous Use.

ABBOTT LABORATORIES, NORTH CHICAGO, IL 60064, USA

APPROVED

SUFENTANIL CITRATE

Injection, USP

50 mcg/mL Sufentanil

WARNING: MAY BE HABIT FORMING

FOR INTRAVENOUS OR EPIDURAL USE

Ampul

Fliptop Vial

Protect from light.

Retain in carton until time of use.

DESCRIPTION

Sufentanil Citrate Injection, USP is a sterile, nonpyrogenic solution of sufentanil citrate in water for injection. Sufentanil Citrate is a potent opioid analgesic which is administered either epidurally or by intravenous injection.

06- 9437 -R2-Rev. Sept., 1996

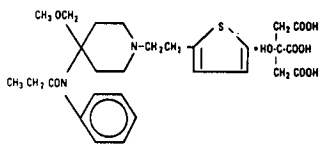
APPROVED

ach mL contains sufentanil citrate equivalent to 50 mcg of entanil. May contain sodium hydroxide and/or hydrochloric acid for adjustment. pH 4.2 (3.5 to 6.0).

he solution contains no bacteriostat, antimicrobial agent or added fer and is intended for use only as a single-use injection. When aller doses are required, the unused portion should be discarded in appropriate manner.

ufentanil Citrate, USP, occurs as a white crystalline powder and is emically designated as *N*-[4-(methyoxymethyl)-1-[2-(2-enyl)ethyl]-4-piperidinyl]-*N*-phenylpropanamide 2-hydroxy-1,2,3-panetricarboxylate (1:1).

he molecular formula of sufentanil citrate is $C_{22}H_{30}N_2O_2S \cdot C_6H_8O_7$ the molecular weight is 578.69. Sufentanil Citrate has the following ıctural formula:



2

CLINICAL PHARMACOLOGY

Pharmacology

Sufentanil citrate is an opioid analgesic. When used in balanced general anesthesia sufentanil has been reported to be as much as 10 times as potent as fentanyl. When administered intravenously as a primary anesthetic agent with 100% oxygen, sufentanil is approximately 5 to 7 times as potent as fentanyl.

Assays of histamine in patients administered sufentanil have shown no elevation in plasma histamine levels and no indication of histamine release.

(See dosage chart for more complete information on the intravenous use of sufentanil.)

Pharmacodynamics

Intravenous Use

At intravenous doses of up to 8 mcg/kg, sufentanil is an analgesic component of general anesthesia; at intravenous doses ≥8 mcg/kg, sufentanil produces a deep level of anesthesia. Sufentanil produces a dose related attenuation of catecholamine release, particularly norepinephrine.

At intravenous dosages of ≥8 mcg/kg, sufentanil produces hypnosis and anesthesia without the use of additional anesthetic agents. A deep level of anesthesia is maintained at these dosages, as demonstrated by EEG patterns. Dosages of up to 25 mcg/kg attenuate the sympathetic response to surgical stress. The catecholamine response, particularly norepinephrine, is further attenuated at doses of sufentanil of 25-30 mcg/kg with hemodynamic stability and preservation of favorable myocardial oxygen balance.

3

Sufentanil has an immediate onset of action, with relatively limited accumulation. Rapid elimination from tissue storage sites allows for relatively more rapid recovery as compared with equipotent dosages of fentanyl. At dosages of 1-2 mcg/kg, recovery times are comparable to those observed with fentanyl; at dosages of > 2-6 mcg/kg, recovery times are comparable to enflurane, isoflurane and fentanyl. Within the anesthetic dosage range of 8-30 mcg/kg of sufentanil, recovery times are more rapid compared to equipotent fentanyl dosages.

The vagolytic effects of pancuronium may produce a dose dependent elevation in heart rate during sufentanil-oxygen anesthesia. The use of moderate doses of pancuronium or of a less vagolytic neuromuscular blocking agent may be used to maintain a stable lower heart rate and blood pressure during sufentanil-oxygen anesthesia. The vagolytic effects of pancuronium may be reduced in patients administered nitrous oxide with sufentanil.

Preliminary data suggest that in patients administered high doses of sufentanil, initial dosage requirements for neuromuscular blocking agents are generally lower as compared to patients given fentanyl or halothane, and comparable to patients given enflurane.

Bradycardia is infrequently seen in patients administered sufentanil-oxygen anesthesia. The use of nitrous oxide with high doses of sufentanil may decrease mean arterial pressure, heart rate and cardiac output.

Sufentanil at 20 mcg/kg has been shown to provide more adequate reduction in intracranial volume than equivalent doses of fentanyl, based upon requirements for furosemide and anesthesia supplementation in one study of patients undergoing craniotomy.

4

During carotid endarterectomy, sufentanil-nitrous oxide/oxygen produced reductions in cerebral blood flow comparable to those of enflurane-nitrous oxide/oxygen. During cardiovascular surgery, sufentanil-oxygen produced EEG patterns similar to fentanyl-oxygen; these EEG changes were judged to be compatible with adequate general anesthesia.

The intraoperative use of sufentanil at anesthetic dosages maintains cardiac output, with a slight reduction in systemic vascular resistance during the initial postoperative period. The incidence of postoperative hypertension, need for vasoactive agents and requirements for postoperative analgesics are generally reduced in patients administered moderate or high doses of sufentanil as compared to patients given inhalation agents.

Skeletal muscle rigidity is related to the dose and speed of administration of sufentanil. This muscular rigidity may occur unless preventative measures are taken (see WARNINGS).

Decreased respiratory drive and increased airway resistance occur with sufentanil. The duration and degree of respiratory depression are dose related when sufentanil is used at sub-anesthetic dosages. At high doses, a pronounced decrease in pulmonary exchange and apnea may be produced.

Epidural Use in Labor and Delivery

Onset of analgesic effect occurs within approximately 10 minutes of administration of epidural doses of sufentanil and bupivacaine. Duration of analgesia following a single epidural injection of 10-15 mcg sufentanil and bupivacaine 0.125% averaged 1.7 hours.

5

During labor and vaginal delivery, the addition of 10-15 mcg sufentanil to 10 mL 0.125% bupivacaine provides an increase in the duration of analgesia compared to bupivacaine without an opioid. Analgesia from 15 mcg sufentanil plus 10 mL 0.125% bupivacaine is comparable to analgesia from 10 mL of 0.25% bupivacaine alone. Apgar scores of neonates following epidural administration of both drugs to women in labor were comparable to neonates whose mothers received bupivacaine without an opioid epidurally.

Pharmacokinetics

Intravenous Use

The pharmacokinetics of intravenous sufentanil can be described as a three-compartment model, with a distribution time of 1.4 minutes, redistribution of 17.1 minutes and an elimination half-life of 164 minutes. The liver and small intestine are the major sites of biotransformation. Approximately 80% of the administered dose is excreted within 24 hours and only 2% of the dose is eliminated as unchanged drug. Plasma protein binding of sufentanil, related to the alpha$_1$ acid glycoprotein concentration, was approximately 93% in healthy males, 91% in mothers and 79% in neonates.

Epidural Use in Labor and Delivery

After epidural administration of incremental doses totaling 5-40 mcg sufentanil during labor and delivery, maternal and neonatal sufentanil plasma concentrations were at or near the 0.05 to 0.1 ng/mL limit of detection, and were slightly higher in mothers than in their infants.

CLINICAL STUDIES

Epidural Use in Labor and Delivery

Epidural sufentanil was tested in 340 patients in two (one single-center and one multi-center) double-blind, parallel studies. Doses ranged from 10 to 15 mcg sufentanil and were delivered in a 10 mL volume of 0.125% bupivacaine with and without epinephrine 1:200,000. In all cases sufentanil was administered following a dose of local anesthetic to test proper catheter placement. Since epidural opioids and local anesthetics potentiate each other, these results many not reflect the dose or efficacy of epidural sufentanil by itself.

Individual doses of 10 -15 mcg sufentanil plus bupivacaine 0.125% with epinephrine provided analgesia during the first stage of labor with a duration of 1-2 hours. Onset was rapid (within 10 minutes). Subsequent doses (equal dose) tended to have shorter duration. Analgesia was profound (complete pain relief) in 80% to 100% of patients and a 25% incidence of pruritus was observed. The duration of initial doses of sufentanil plus bupivacaine with epinephrine is approximately 95 minutes, and of subsequent doses, 70 minutes.

There are insufficient data to critically evaluate neonatal neuromuscular and adaptive capacity following recommended doses of maternally administered epidural sufentanil with bupivacaine. However, if larger than recommended doses are used for combined local and systemic analgesia, e.g. after administration of a single dose of 50 mcg epidural sufentanil during delivery, then impaired neonatal adaption to sound and light can be detected for 1 to 4 hours and if a

dose of 80 mcg is used impaired neuromuscular coordination can be detected for more than 4 hours.

INDICATIONS AND USAGE

Sufentanil Citrate Injection, USP is indicated for intravenous administration:

As an analgesic adjunct in the maintenance of balanced general anesthesia in patients who are intubated and ventilated.

As a primary anesthetic agent for the induction and maintenance of anesthesia with 100% oxygen in patients undergoing major surgical procedures, in patients who are intubated and ventilated, such as cardiovascular surgery or neurosurgical procedures in the sitting position, to provide favorable myocardial and cerebral oxygen balance or when extended postoperative ventilation is anticipated.

Sufentanil Citrate Injection, USP is indicated for epidural administration as an analgesic combined with low dose bupivacaine, usually 12.5 mg per administration, during labor and vaginal delivery.

SEE DOSAGE AND ADMINISTRATION SECTION FOR MORE COMPLETE INFORMATION ON THE USE OF SUFENTANIL.

CONTRAINDICATIONS

Sufentanil Citrate Injection is contraindicated in patients with known hypersensitivity to the drug or known intolerance to other opioid agonists.

WARNINGS

SUFENTANIL CITRATE INJECTION SHOULD BE ADMINISTERED ONLY BY PERSONS SPECIFICALLY TRAINED IN THE USE OF INTRAVENOUS

AND EPIDURAL ANESTHETICS AND MANAGEMENT OF THE RESPIRATORY EFFECTS OF POTENT OPIOIDS.

AN OPIOID ANTAGONIST, RESUSCITATIVE AND INTUBATION EQUIPMENT AND OXYGEN SHOULD BE READILY AVAILABLE.

PRIOR TO CATHETER INSERTION, THE PHYSICIAN SHOULD BE FAMILIAR WITH PATIENT CONDITIONS (SUCH AS INFECTION AT THE INJECTION SITE, BLEEDING DIATHESIS, ANTICOAGULANT THERAPY ETC.) WHICH CALL FOR SPECIAL EVALUATION OF THE BENEFIT VERSUS RISK POTENTIAL.

Intravenous Use

Intravenous administration or unintentional intravascular injectio during epidural administration of sufentanil citrate may cause skelet muscle rigidity, particularly of the truncal muscles. The incidence an severity of muscle rigidity is dose related. Administration of sufentan citrate may produce muscular rigidity with a more rapid onset of actio than that seen with fentanyl. Sufentanil may produce muscular rigidit that involves the skeletal muscles of the neck and extremities. As wit fentanyl, muscular rigidity has been reported to occur or rec infrequently in the extended postoperative period. The incidence muscular rigidity associated with intravenous sufentanil can b reduced by: 1) administration of up to 1/4 of the full paralyzing dose a nondepolarizing neuromuscular blocking agent just prior administration of sufentanil citrate at dosages of up to 8 mcg/k 2) administration of a full paralyzing dose of a neuromuscular blockin agent following loss of consciousness when sufentanil is used anesthetic dosages (above 8 mcg/kg) titrated by slow intraveno

AND EPIDURAL ANESTHETICS AND MANAGEMENT OF THE RESPIRATORY EFFECTS OF POTENT OPIOIDS.

AN OPIOID ANTAGONIST, RESUSCITATIVE AND INTUBATION EQUIPMENT AND OXYGEN SHOULD BE READILY AVAILABLE.

PRIOR TO CATHETER INSERTION, THE PHYSICIAN SHOULD BE FAMILIAR WITH PATIENT CONDITIONS (SUCH AS INFECTION AT THE INJECTION SITE, BLEEDING DIATHESIS, ANTICOAGULANT THERAPY, ETC.) WHICH CALL FOR SPECIAL EVALUATION OF THE BENEFIT VERSUS RISK POTENTIAL.

Intravenous Use

Intravenous administration or unintentional intravascular injection during epidural administration of sufentanil citrate may cause skeletal muscle rigidity, particularly of the truncal muscles. The incidence and severity of muscle rigidity is dose related. Administration of sufentanil citrate may produce muscular rigidity with a more rapid onset of action than that seen with fentanyl. Sufentanil may produce muscular rigidity that involves the skeletal muscles of the neck and extremities. As with fentanyl, muscular rigidity has been reported to occur or recur infrequently in the extended postoperative period. The incidence of muscular rigidity associated with intravenous sufentanil can be reduced by: 1) administration of up to 1/4 of the full paralyzing dose of a nondepolarizing neuromuscular blocking agent just prior to administration of sufentanil citrate at dosages of up to 8 mcg/kg, 2) administration of a full paralyzing dose of a neuromuscular blocking agent following loss of consciousness when sufentanil is used in anesthetic dosages (above 8 mcg/kg) titrated by slow intravenous

infusion, or, 3) simultaneous administration of sufentanil and a full paralyzing dose of a neuromuscular blocking agent when sufentanil is used in rapidly administered anesthetic dosages (above 8 mcg/kg).

The neuromuscular blocking agents used should be compatible with the patient's cardiovascular status. Adequate facilities should be available for postoperative monitoring and ventilation of patients administered sufentanil. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.

PRECAUTIONS

General: The initial dose of sufentanil should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining supplemental doses.

Vital signs should be monitored routinely.

Nitrous oxide may produce cardiovascular depression when given with high doses of sufentanil (see CLINICAL PHARMACOLOGY).

Bradycardia has been reported infrequently with sufentanil-oxygen anesthesia and has been responsive to atropine.

Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists such as naloxone. Because the duration of respiratory depression produced by sufentanil may last longer than the duration of the opioid antagonist action, appropriate surveillance should be maintained. As with all potent opioids, profound analgesia is accompanied by respiratory depression and diminished sensitivity to CO_2 stimulation which may persist into or recur in the postoperative period. Respiratory depression may be enhanced when sufentanil is administered in combination with volatile inhalational agents and/or

other central nervous system depressants such as barbiturates, tranquilizers, and other opioids. Appropriate postoperative monitoring should be employed to ensure that adequate spontaneous breathing is established and maintained prior to discharging the patient from the recovery area. Respiration should be closely monitored following each administration of an epidural injection of sufentanil.

Proper placement of the needle or catheter in the epidural space should be verified before sufentanil is injected to assure that unintentional intravascular or intrathecal administration does not occur. Unintentional intravascular injection of sufentanil could result in a potentially serious overdose, including acute truncal muscular rigidity and apnea. Unintentional intrathecal injection of the full sufentanil/bupivacaine epidural doses and volume could produce effects of high spinal anesthesia including prolonged paralysis and delayed recovery. If analgesia is inadequate, the placement and integrity of the catheter should be verified prior to the administration of any additional epidural medications. Sufentanil should be administered epidurally by slow injection.

Neuromuscular Blocking Agents: The hemodynamic effects and degree of skeletal muscle relaxation required should be considered in the selection of a neuromuscular blocking agent. High doses of pancuronium may produce increases in heart rate during sufentanil-oxygen anesthesia. Bradycardia and hypotension have been reported with other muscle relaxants during sufentanil-oxygen anesthesia; this effect may be more pronounced in the presence of calcium channel and/or beta blockers. Muscle relaxants with no clinically significant effect on heart rate (at recommended doses) would not counteract the

vagotonic effect of sufentanil, therefore a lower heart rate
expected. Rare reports of bradycardia associated
concomitant use of succinylcholine and sufentanil have been

Interaction With Calcium Channel and Beta Blockers: The
and degree of bradycardia and hypotension during induc
sufentanil may be greater in patients on chronic calcium cha
beta blocker therapy. (See Neuromuscular Blocking Agents).

Interaction With Other Central Nervous System Depressants:
magnitude and duration of central nervous system and cardi
effects may be enhanced when sufentanil is administered to
receiving barbiturates, tranquilizers, other opioids, general an
or other CNS depressants. In such cases of combined treat
dose of sufentanil and/or these agents should be reduced.

The use of benzodiazepines with sufentanil during induc
result in a decrease in mean arterial pressure and systemic
resistance.

Head Injuries: Sufentanil may obscure the clinical course of
with head injuries.

Impaired Respiration: Sufentanil should be used with c
patients with pulmonary disease, decreased respiratory re
potentially compromised respiration, In such patients, opi
additionally decrease respiratory drive and increase
resistance. During anesthesia, this can be managed by as
controlled respiration.

Impaired Hepatic or Renal Function: In patients with liver
dysfunction, sufentanil citrate should be administered with ca

nervous system depressants such as barbiturates, nd other opioids. Appropriate postoperative monitoring oyed to ensure that adequate spontaneous breathing is maintained prior to discharging the patient from the Respiration should be closely monitored following each of an epidural injection of sufentanil.

ment of the needle or catheter in the epidural space rified before sufentanil is injected to assure that ntravascular or intrathecal administration does not tional intravascular injection of sufentanil could result in serious overdose, including acute truncal muscular pnea. Unintentional intrathecal injection of the full ivacaine epidural doses and volume could produce n spinal anesthesia including prolonged paralysis and very. If analgesia is inadequate, the placement and catheter should be verified prior to the administration of epidural medications. Sufentanil should be administered slow injection.

ar Blocking Agents: The hemodynamic effects and letal muscle relaxation required should be considered in of a neuromuscular blocking agent. High doses of may produce increases in heart rate during sufentanil-thesia. Bradycardia and hypotension have been reported uscle relaxants during sufentanil-oxygen anesthesia; this e more pronounced in the presence of calcium channel blockers. Muscle relaxants with no clinically significant art rate (at recommended doses) would not counteract the

vagotonic effect of sufentanil, therefore a lower heart rate would be expected. Rare reports of bradycardia associated with the concomitant use of succinylcholine and sufentanil have been reported.

Interaction With Calcium Channel and Beta Blockers: The incidence and degree of bradycardia and hypotension during induction with sufentanil may be greater in patients on chronic calcium channel and beta blocker therapy. (See Neuromuscular Blocking Agents).

Interaction With Other Central Nervous System Depressants: Both the magnitude and duration of central nervous system and cardiovascular effects may be enhanced when sufentanil is administered to patients receiving barbiturates, tranquilizers, other opioids, general anesthetics or other CNS depressants. In such cases of combined treatment, the dose of sufentanil and/or these agents should be reduced.

The use of benzodiazepines with sufentanil during induction may result in a decrease in mean arterial pressure and systemic vascular resistance.

Head Injuries: Sufentanil may obscure the clinical course of patients with head injuries.

Impaired Respiration: Sufentanil should be used with caution in patients with pulmonary disease, decreased respiratory reserve or potentially compromised respiration. In such patients, opioids may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration.

Impaired Hepatic or Renal Function: In patients with liver or kidney dysfunction, sufentanil citrate should be administered with caution due

to the importance of these organs in the metabolism and excretion of sufentanil.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No long-term animal studies of sufentanil have been performed to evaluate carcinogenic potential. The micronucleus test in female rats revealed that single intravenous doses of sufentanil as high as 80 mcg/kg (approximately 2.5 times the upper human intravenous dose) produced no structural chromosome mutations. The Ames *Salmonella typhimurium* metabolic activating test also revealed no mutagenic activity. See Animal Toxicology for reproduction studies in rats and rabbits.

Pregnancy: Teratogenic Effects:

Pregnancy Category C: Sufentanil has been shown to have an embryocidal effect in rats and rabbits when given in doses 2.5 times the upper human intravenous dose for a period of 10 days to over 30 days. These effects were most probably due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug.

No evidence of teratogenic effects have been observed after administration of sufentanil citrate in rats or rabbits.

Labor and Delivery: The use of epidurally administered sufentanil in combination with bupivacaine 0.125% with or without epinephrine is indicated for labor and delivery. (See INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION sections.) Sufentanil is not recommended for intravenous use or for use of larger epidural doses during labor and delivery because of potential risks to the newborn

infant after delivery. In clinical trials, one case of severe fetal bradycardia associated with maternal hypotension was reported within 8 minutes of maternal administration of sufentanil 15 mcg plus bupivacaine 0.125% (10 mL total volume).

Nursing Mothers: It is not known whether sufentanil is excreted in human milk. Because fentanyl analogs are excreted in human milk, caution should be exercised when sufentanil citrate is administered to a nursing woman.

Pediatric Use: The safety and efficacy of intravenous sufentanil citrate in pediatric patients under two years of age undergoing cardiovascular surgery has been documented in a limited number of cases.

Animal Toxicology: The intravenous LD_{50} of sufentanil is 16.8 to 18.0 mg/kg in mice, 11.8 to 13.0 mg/kg in guinea pigs and 10.1 to 19.5 mg/kg in dogs. Reproduction studies performed in rats and rabbits given doses of up to 2.5 times the upper human intravenous dose for a period of 10 to over 30 days revealed high maternal mortality rates due to decreased food consumption and anoxia, which preclude any meaningful interpretation of the results. Epidural and intrathecal injections of sufentanil in dogs and epidural injections in rats were not associated with neurotoxicity.

ADVERSE REACTIONS

The most common adverse reactions of opioids are respiratory depression and skeletal muscle rigidity, particularly of the truncal muscles. Sufentanil may produce muscular rigidity that involves the

skeletal muscles of the neck and extremities. See CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS on the management of respiratory depression and skeletal muscle rigidity. Urinary retention has been associated with the use of epidural opioids but was not reported in the clinical trials of epidurally administered sufentanil due to the use of indwelling catheters. The incidence of urinary retention in patients without urinary catheters receiving epidural sufentanil is unknown; return of normal bladder activity may be delayed.

The following adverse reaction information is derived from controlled clinical trials in 320 patients who received intravenous sufentanil during surgical anesthesia and in 340 patients who received epidural sufentanil plus bupivacaine 0.125% for analgesia during labor and is presented below. Based on the observed frequency, none of the reactions occurring with an incidence less than 1% were observed during clinical trials of epidural sufentanil used during labor and delivery (N=340).

In general cardiovascular and musculoskeletal adverse experiences were not observed in clinical trials of epidural sufentanil. Hypotension was observed 7 times more frequently in intravenous trials than in epidural trials. The incidence of central nervous system, dermatological and gastrointestinal adverse experiences was approximately 4 to 25 times higher in studies of epidural use in labor and delivery.

Probably Causally Related: Incidence Greater than 1% — Derived from clinical trials (See preceding paragraph)

Cardiovascular: bradycardia*, hypertension*, hypotension*.

Musculoskeletal: chest wall rigidity*.

Central Nervous System: somnolence*.

Dermatological: pruritus (25%).

Gastrointestinal: nausea*, vomiting*.

* Incidence 3% to 9%.

Probably Causally Related: Incidence Less than 1% — Derived from clinical trials (Adverse events reported in post-marketing surveillance, not seen in clinical trials, are *italicized.*)

Body as a Whole: anaphylaxis.

Cardiovascular: arrhythmia*, tachycardia*, *cardiac arrest.*

Central Nervous System: chills*.

Dermatological: erythema*.

Musculoskeletal: skeletal muscle rigidity of neck and extremities.

Respiratory: apnea*, bronchospasm*, postoperative respiratory depression*.

Miscellaneous: intraoperative muscle movement*.

*0.3% to 1%.

DRUG ABUSE AND DEPENDENCE

Sufentanil Citrate Injection is a Schedule II controlled drug substance that can produce drug dependence of the morphine type and therefore has the potential for being abused.

OVERDOSAGE

Overdosage is manifested by an extension of the pharmacological

actions of sufentanil (see CLINICAL PHARMACOLOG potent opioid analgesics. The most serious and sign overdose for both intravenous and epidural administrat is respiratory depression. Intravenous administratio antagonist such as naloxone should be employed as a to manage respiratory depression. The duration depression following overdosage with sufentanil may be duration of action of the opioid antagonist. Administrat antagonist should not preclude more immediate coun the event of overdosage, oxygen should be administere assisted or controlled as indicated for hypoventilatio patent airway must be maintained, and a nasopharyn endotracheal tube may be indicated. If depressed associated with muscular rigidity, a neuromuscular bloc be required to facilitate assisted or controlled respirati fluids and vasopressors for the treatment of hypoten supportive measures may be employed.

DOSAGE AND ADMINISTRATION

The dosage of sufentanil should be individualized according to body weight, physical status, underlyin condition, use of other drugs, and type of surgical anesthesia. In obese patients (more than 20% above i weight), the dosage of sufentanil citrate should be dete basis of lean body weight. Dosage should be reduced debilitated patients (see PRECAUTIONS).

Vital signs should be monitored routinely.

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actions of sufentanil (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. The most serious and significant effect of overdose for both intravenous and epidural administration of sufentanil is respiratory depression. Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression. The duration of respiratory depression following overdosage with sufentanil may be longer than the duration of action of the opioid antagonist. Administration of an opioid antagonist should not preclude more immediate countermeasures. In the event of overdosage, oxygen should be administered and ventilation assisted or controlled as indicated for hypoventilation or apnea. A patent airway must be maintained, and a nasopharyngeal airway or endotracheal tube may be indicated. If depressed respiration is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled respiration. Intravenous fluids and vasopressors for the treatment of hypotension and other supportive measures may be employed.

DOSAGE AND ADMINISTRATION

The dosage of sufentanil should be individualized in each case according to body weight, physical status, underlying pathological condition, use of other drugs, and type of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of sufentanil citrate should be determined on the basis of lean body weight. Dosage should be reduced in elderly and debilitated patients (see PRECAUTIONS).

Vital signs should be monitored routinely.

Intravenous Use

Sufentanil Citrate may be administered intravenously by slow injection or infusion 1) in doses of up to 8 mcg/kg as an analgesic adjunct to general anesthesia, and 2) in doses ≥ 8 mcg/kg as a primary anesthetic agent for induction and maintenance of anesthesia (see Dosage Range Chart).

If benzodiazepines, barbiturates, inhalation agents, other opioids or other central nervous system depressants are used concomitantly, the dose of sufentanil and/or these agents should be reduced (see PRECAUTIONS). In all cases dosage should be titrated to individual patient response.

Usage In Children: For induction and maintenance of anesthesia in children less than 12 years of age undergoing cardiovascular surgery, an anesthetic dose of 10-25 mcg/kg administered with 100% oxygen is generally recommended. Supplemental dosages of up to 25-50 mcg are recommended for maintenance, based on response to initial dose and as determined by changes in vital signs indicating surgical stress or lightening of anesthesia.

Premedication: The selection of preanesthetic medications should be based upon the needs of the individual patient.

Neuromuscular Blocking Agents: The neuromuscular blocking agent selected should be compatible with the patient's condition, taking into account the hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required (see CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS).

ADULT DOSAGE RANGE CHART FOR INTRAVENOUS USE (expressed as Sufentanil)
ANALGESIC COMPONENT TO GENERAL ANESTHESIA
*** Total Dosage Requirements of 1 mcg/kg/hr or Less are Recommended**

Total Dosage	ANALGESIC DOSAGES	Maintenance Dosage
Incremental or Infusion:		**Incremental:**
1-2 mcg/kg (expected duration of anesthesia 1-2 hours). Approximately 75% or more of total sufentanil dosage may be administered prior to intubation by either slow injection or infusion titrated to individual patient response. Dosages in this range are generally administered with nitrous oxide/oxygen in patients undergoing general surgery in which endotracheal intubation and mechanical ventilation are required.		**10-25 mcg (0.2-0.5 mL)** may be administered in increments as needed changes in vital signs indicate surgical stress or lightening of dosages should be individualized and adjusted to remaining operati
		Infusion:
		Sufentanil may be administered as an intermittent or continuous response to signs of lightening of analgesia. In absence of signs o infusion rates should always be adjusted downward until there is so stimulation. Maintenance infusion rates should be adjusted based up sufentanil so that the total dose does not exceed 1 mcg/kg/hr of Dosage should be individualized and adjusted to remaining operative
Incremental or Infusion:		**Incremental:**
2-8 mcg/kg (expected duration of anesthesia 2-8 hours). Approximately 75% or less of the total calculated sufentanil dosage may be administered by slow injection or infusion prior to intubation, titrated to individual patient response. Dosages in this range are generally administered with nitrous oxide/oxygen in patients undergoing more complicated major surgical procedures in which endotracheal intubation and mechanical ventilation are required. At dosages in this range, sufentanil has been shown to provide some attenuation of sympathetic reflex activity in response to surgical stimuli, provide hemodynamic stability, and provide relatively rapid recovery.		**10-50 mcg (0.2-1 mL)** may be administered in increments as needed changes in vital signs indicate surgical stress or lightening of ar dosages should be individualized and adjusted to the remaining opera
		Infusion:
		Sufentanil may be administered as an intermittent or continuous response to signs of lightening of analgesia. In the absence of signs of infusion rates should always be adjusted downward until there is som stimulation. Maintenance infusion rates should be adjusted based upo sufentanil so that the total dose does not exceed 1 mcg/kg/hr of ex Dosage should be individualized and adjusted to remaining operative ti

CHART FOR INTRAVENOUS USE (expressed as Sufentanil)
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Maintenance Dosage

ANALGESIC DOSAGES

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Incremental:

10-25 mcg (0.2-0.5 mL) may be administered in increments as needed when movement and/or changes in vital signs indicate surgical stress or lightening of analgesia. Supplemental dosages should be individualized and adjusted to remaining operative time anticipated.

Infusion:

Sufentanil may be administered as an intermittent or continuous infusion as needed in response to signs of lightening of analgesia. In absence of signs of lightening of analgesia infusion rates should always be adjusted downward until there is some response to surgical stimulation. Maintenance infusion rates should be adjusted based upon the induction dose of sufentanil so that the total dose does not exceed 1 mcg/kg/hr of expected surgical time. Dosage should be individualized and adjusted to remaining operative time anticipated.

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Incremental:

10-50 mcg (0.2-1 mL) may be administered in increments as needed when movement and/or changes in vital signs indicate surgical stress or lightening of analgesia. Supplemental dosages should be individualized and adjusted to the remaining operative time anticipated.

Infusion:

Sufentanil may be administered as an intermittent or continuous infusion as needed in response to signs of lightening of analgesia. In the absence of signs of lightening of analgesia, infusion rates should always be adjusted downward until there is some response to surgical stimulation. Maintenance infusion rates should be adjusted based upon the induction dose of sufentanil so that the total dose does not exceed 1 mcg/kg/hr of expected surgical time. Dosage should be individualized and adjusted to remaining operative time anticipated.

ADULT DOSAGE RANGE CHART FOR INTRAVENOUS USE (expressed as Sufentanil)
ANALGESIC COMPONENT TO GENERAL ANESTHESIA
* Total Dosage Requirements of 1 mcg/kg/hr or Less are Recommended

Total Dosage	Maintenance Dosage
ANESTHETIC DOSAGES	
Incremental or Infusion:	**Incremental:**
8-30 mcg/kg (anesthetic doses). At this anesthetic dosage range sufentanil is generally administered as a slow injection, as an infusion, or as an injection followed by an infusion. Sufentanil with 100% oxygen and a muscle relaxant has been found to produce sleep at dosages ≥ 8 mcg/kg and to maintain a deep level of anesthesia without the use of additional anesthetic agents. The addition of N_2O to these dosages will reduce systolic blood pressure. At dosages in this range of up to 25 mcg/kg, catecholamine release is attenuated. Dosages of 25-30 mcg/kg have been shown to block sympathetic response including catecholamine release. High doses are indicated in patients undergoing major surgical procedures, in which endotracheal intubation and mechanical ventilation are required, such as cardiovascular surgery and neurosurgery in the sitting position with maintenance of favorable myocardial and cerebral oxygen balance. Postoperative observation is essential and postoperative mechanical ventilation may be required at the higher dosage range due to extended postoperative respiratory depression. Dosage should be titrated to individual patient response.	Depending on the initial dose, maintenance doses of 0.5-10 mcg/kg may be administered by slow injection in anticipation of surgical stress such as incision, sternotomy or cardiopulmonary bypass. **Infusion:** Sufentanil may be administered by continuous or intermittent infusion as needed in response to signs of lightening of anesthesia. In the absence of lightening of anesthesia, infusion rates should always be adjusted downward until there is some response to surgical stimulation. The maintenance infusion rate for sufentanil should be based upon the induction dose so that the total dose for the procedure does not exceed 30 mcg/kg.

In patients administered high doses of sufenta
essential that qualified personnel and adequate facilit
for the management of postoperative respiratory depr

Also see WARNINGS and PRECAUTIONS sections.

For purposes of administering small volumes of sufentar
accurately, the use of a tuberculin syringe or equivalent is

Epidural Use in Labor and Delivery

Proper placement of the needle or catheter in the
should be verified before sufentanil is injected
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rigidity and apnea. Unintentional intrathecal injec
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delayed recovery. If analgesia is inadequate, the
integrity of the catheter should be verified prior to the
any additional epidural medications. Sufentanil should
by slow injection. Respiration should be closely mo
each administration of an epidural injection of sufent

Dosage for Labor and Delivery: The recommended do
10-15 mcg administered with 10 mL bupivacaine 0.125
epinephrine. Sufentanil and bupivacaine should be
before administration. Doses can be repeated twice (f
doses) at not less than one-hour intervals until delive

In patients administered high doses of sufentanil citrate, it is essential that qualified personnel and adequate facilities are available for the management of postoperative respiratory depression.

Also see WARNINGS and PRECAUTIONS sections.

For purposes of administering small volumes of sufentanil citrate injection accurately, the use of a tuberculin syringe or equivalent is recommended.

Epidural Use in Labor and Delivery

Proper placement of the needle or catheter in the epidural space should be verified before sufentanil is injected to assure that unintentional intravascular or intrathecal administration does not occur. Unintentional intravascular injection of sufentanil could result in a potentially serious overdose, including acute truncal muscular rigidity and apnea. Unintentional intrathecal injection of the full sufentanil, bupivacaine epidural doses and volume could produce effects of high spinal anesthesia including prolonged paralysis and delayed recovery. If analgesia is inadequate, the placement and integrity of the catheter should be verified prior to the administration of any additional epidural medications. Sufentanil should be administered by slow injection. Respiration should be closely monitored following each administration of an epidural injection of sufentanil.

Dosage for Labor and Delivery: The recommended dosage is sufentanil 10-15 mcg administered with 10 mL bupivacaine 0.125% with or without epinephrine. Sufentanil and bupivacaine should be mixed together before administration. Doses can be repeated twice (for a total of three doses) at not less than one-hour intervals until delivery.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED

Sufentanil Citrate Injection, USP equivalent to 50 mcg/mL sufentanil is supplied in the following single-use containers:

List Number	Container	Container Size	Total Sufentanil per Container
3380	Ampul	1 mL fill in 1 mL	50 mcg
3380	Ampul	2 mL fill in 2 mL	100 mcg
3380	Ampul	5 mL fill in 5 mL	250 mcg
3382	Fliptop Vial	1 mL fill in 2 mL	50 mcg
3382	Fliptop Vial	2 mL fill in 2 mL	100 mcg
3382	Fliptop Vial	5 mL fill in 5 mL	250 mcg

Protect from light. Retain in carton until time of use.

Store at controlled room temperature 15° to 30°C (59° to 86°F).

Caution: Federal (USA) law prohibits dispensing without prescription.

Printed in USA

ABBOTT LABORATORIES, NORTH CHICAGO, IL 60064, USA

SUFENTANIL CITRATE

CII

Injection, USP

50 mcg/mL Sufentanil

WARNING: MAY BE HABIT FORMING

FOR INTRAVENOUS OR EPIDURAL USE

Ampul

Fliptop Vial

Protect from light.

Retain in carton until time of use.

DESCRIPTION

Sufentanil Citrate Injection, USP is a sterile, nonpyrogenic solution of sufentanil citrate in water for injection. Sufentanil Citrate is a potent opioid analgesic which is administered either epidurally or by intravenous injection.

06- 9437 -R2-Rev. Sept., 1996

APPROVED

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074534

CHEMISTRY REVIEW(S)

1. CHEMIST'S REVIEW NO. 4

2. ANDA # 74-534

3. NAME AND ADDRESS OF APPLICANT
Abbott Laboratories
Attention: Thomas F. Willer, Ph.D.
One Abbott Park Road
Abbott Park, Illinois 60064

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Sufentanil Citrate Injection

9. AMENDMENTS AND OTHER DATES:

Firm		FDA	
Original sub.	08/15/94	RF Letter	10/06/94
Amendment	10/14/94	Ack. letter	11/16/94
Amendment	06/28/95	N/A Letter	03/14/95
Amendment	02/23/96	N/A Letter	12/15/95
Amendment	09/03/96	N/A Letter	08/01/96
Amendment	10/09/96		
Telephone Am.	12/05/96		

10. PHARMACOLOGICAL CATEGORY
Narcotic analgesic

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

(b)4 - Confidential Business

13. DOSAGE FORM
Injectable

14. POTENCY
50 mcg/mL

15. CHEMICAL NAME AND STRUCTURE
$C_{22}H_{30}N_2O_2S.C_6H_8O_7$ USP article

17. COMMENTS
See text of review.

18. CONCLUSIONS AND RECOMMENDATIONS
Approvable.

19. REVIEWER:
Andrew J. Langowski

DATE COMPLETED:
9/30/96

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074534

BIOEQUIVALENCE REVIEW(S)

DW

DIVISION REVIEW SUMMARY

ANDA: 74-534

FIRM: Abbott Laboratories, Inc.

DOSAGE FORM: Injection STRENGTH: 50 mcg/mL

DRUG: Sufentanil Citrate

cGMP STATEMENT/EIR UPDATE STATUS: Acceptable 7/1/96.

BIO STUDY INFORMATION: Bio-waiver granted 3/2/95.

METHODS VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S)

Drug substance and drug product are compendial articles. Validation not required.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION? yes

The containers used in the stability study are of the same size and material as those described in the container section. The firm submitted accelerated stability data for the product packaged in all container sizes.

The firm requests an expiration date of 24 months based on the data submitted.

The stability tests and specifications are indicated in the following table:

TEST	METHOD	SPECIFICATION
Assay (Sufentanil)	C-1528	
Degradant (Single Largest)	C-1528	
Total Degradants	C-1528	
pH	C-0021	
Appearance	P-0842	
Particulates	P-1078A	
Bacterial Endotoxins	B-0913	
Sterility	M-0073	

LABELING: Acceptable 10/15/96.

STERILIZATION VALIDATION: Acceptable 10/3/96.

SIZE OF BIO BATCH -

No information on bio-batch since a waiver was granted.

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH WERE THEY MANUFACTURED VIA SAME PROCESS?)

The size of stability batch #84-570-DK is [redacted] The batch was split into [redacted] and packaged into 4 different container configurations (1 mL, 2 mL, 5 mL vials and 5 mL ampule). Stability batch #89-144-DK was [redacted] and split-filled into 1 mL and 2 mL ampules.

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?

List	Description	Content	Proposed Size
3382	1 mL vial	50 mcg	[redacted] (b)4 - Confidential Business
3382	2 mL vial	100 mcg	
3382	5 mL vial	250 mcg	
3380	1 mL ampul	50 mcg	
3380	2 mL ampul	100 mcg	
3380	5 mL ampul	250 mcg	

RECOMMENDATION: Approvable

SIGNATURE: DATE: